Cytotoxic Compounds. Part X.[1] Carbamates derived from *NN*-Bis-(2-chloroethyl)-*m*- and *NN*-Bis-(2-chloroethyl)-*p*-phenylenediamine

By **L. N. Owen*** and **R. Sridhar**, Department of Chemistry, Imperial College, London S.W.7

Urethanes have been prepared by reaction of the amines *m*-RNH_2 or *p*-RNH_2 [$R = C_6H_4{\cdot}N(CH_2{\cdot}CH_2Cl)_2$] with chloroformates. The products, after removal of protecting groups, include *p*-$RNH{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2H$ (*o*-, *m*-, and *p*-), *m*-$RNH{\cdot}CO{\cdot}O{\cdot}C_6H_4{\cdot}CO_2H$(*m*-), *O*-(*p*-$RNH{\cdot}CO$)-serine, and *O*-(*p*-$RNH{\cdot}CO$)-threonine. Terephthalic amides, (*p*-$RNH{\cdot}CO)_2C_6H_4$ and (*p*-$RNH{\cdot}CO)C_6H_4{\cdot}CO_2Me$, and phthalimides, $C_6H_4(CO)_2NR$ (*m*- and *p*-), are also described.

An earlier paper [2] described the synthesis of a number of urethanes derived from *NN*-bis-(2-chloroethyl)-*p*-phenylenediamine (I) and from *p*-(bis-2-chloroethylamino)-phenol (II); of these compounds, *p*-(bis-2-chloroethylamino)phenyl *N*-(*p*-carboxyphenyl)carbamate (III) has proved to be of particular interest because it possesses a high degree of selectivity of action against the Walker 256 tumour.[3] It was therefore important to prepare the 'reversed' urethane (V), and this was readily effected by reaction of *p*-methoxycarbonylphenyl chloroformate [4a] with the amine (I) to give the methyl ester (IV), followed by brief hydrolysis with a mixture of acetic and hydrochloric acids. Similarly, *o*- [4b] and *m*-methoxycarbonylphenyl chloroformates gave the urethanes (VI) and (IX), of which the former, no doubt for steric reasons, was resistant to selective hydrolysis, whereas the latter readily gave the acid (X). By the use of *o*-benzyloxycarbonylphenyl chloroformate, however, the benzyl ester (VII) was obtained, and this, on hydrogenolysis, furnished the acid (VIII).

To replace the aminobenzoic acid grouping in the urethanes mentioned by a natural α-amino-acid, the mustard amine (I) was condensed with *N*-benzyloxycarbonyl-*O*-chloroformyl-DL-serine methyl ester [5a] to give the carbamate (XI), which on hydrogenolysis gave the amino-ester (XII). This could not be selectively hydrolysed, and the synthesis was accordingly modified to use the chloroformate derived from *N*-benzyloxycarbonyl-DL-serine benzyl ester,[5a] the benzyl ester (XIII) thereby being obtained. Hydrogenolysis over palladium in methanol–ethyl acetate removed only one protecting group and gave the acid (XIV), but when the hydrogenolysis was carried out in the presence of hydrochloric acid the free amino-acid (XV) was obtained. In a similar fashion, the chloroformate prepared from *N*-benzyloxycarbonyl-DL-threonine benzyl ester [5a] afforded the urethane (XVI), from which the amino-acid (XVII) was obtained by hydrogenolysis in the presence of hydrochloric acid. The chloroformate from *N*-benzyloxycarbonyl-L-tyrosine benzyl ester [5b] likewise gave a urethane (XVIII), but the yield was poor and the hydrogenolysis was not attempted.

An analogous series of compounds could be considered in which the orientation of the mustard portion is other than *para*. By using the methods described above for the *para* series, the *meta*-analogue of the amine (I), prepared by a slight modification of the published process,[6] was converted into the *meta*-mustard isomers of the urethanes (VII), (IX), (X), and (XIII). Some simple urethanes (XIX) were also prepared.

In biological tests,[3] the methyl ester (IV) is outstandingly effective in bringing about regression of the Walker tumour. Removal of the phenolic oxygen atom from this compound would leave the structure (XX), now an amide derived from terephthalic acid. Since certain non-mustard amides of terephthalic acid possess anti-tumour activity,[7] the biological properties of compound (XX) would be of interest. Preparation of the acid chloride of methyl hydrogen terephthalate was attempted by each of the reported procedures,[8-10] but the only one to give a reasonable yield was the treatment of terephthaloyl chloride with methanol (1 mol.).[8] Condensation with the *p*-amino-mustard (I) then gave a mixture which, after repeated chromatography, yielded the desired amide (XX), the major product being the diamide (XXI), which was readily obtained also from terephthaloyl chloride. Reaction of the easily prepared [11] acid chloride of methyl hydrogen phthalate with both the *p*- and the *m*-amino-mustard gave only the cyclic imides (XXII) and (XXIII) respectively.

EXPERIMENTAL

Unless otherwise specified, i.r. spectra were measured in chloroform.

NN-*Bis*-(2-*hydroxyethyl*)-m-*nitroaniline*.—Ethylene oxide (25 c.c.), *m*-nitroaniline (5·0 g.), and 40% acetic acid (40

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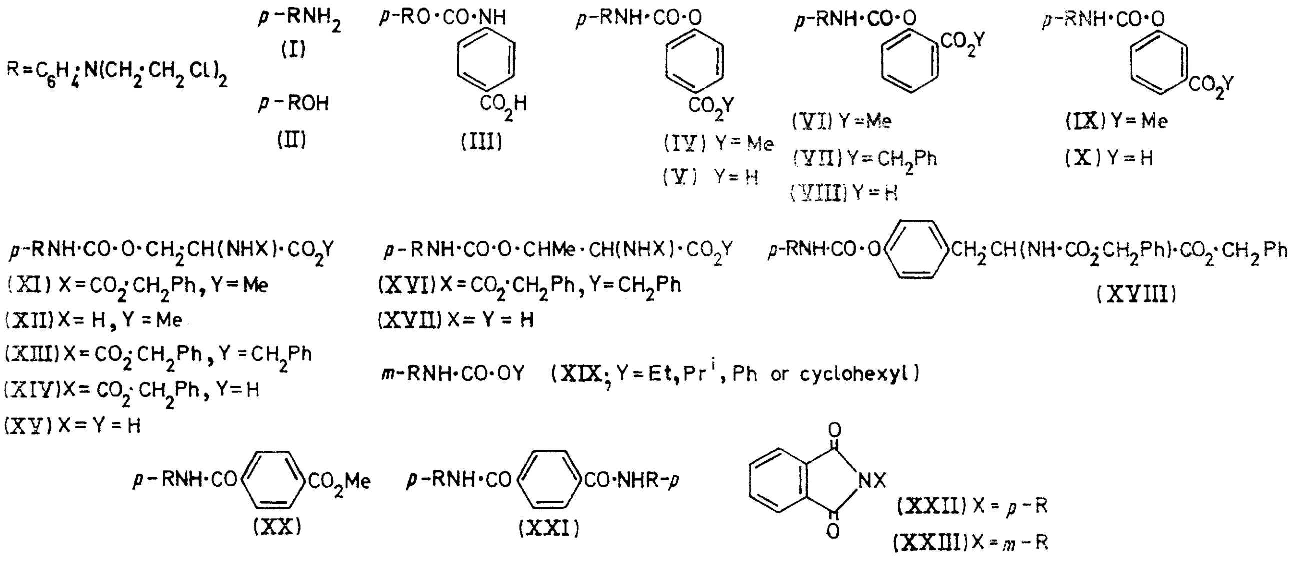
c.c.) were mixed at 0° and then stirred overnight to give a clear solution. This was neutralised with aqueous sodium carbonate, whereupon a yellow solid was precipitated, which gave the diol (4·3 g.), m.p. 98° (from ethanol) (lit.,[12] m.p. 98°).

NN-*Bis*-(2-*chloroethyl*)-m-*nitroaniline*.—Phosphoryl chloride (5·0 g.) was slowly added to a stirred suspension of the diol (4·0 g.) in 1,2-dichloroethane (30 c.c.). The mixture was boiled under reflux for 6 hr. and then concentrated to a viscid oil, which was extracted with boiling 1,2-dichloroethane. The dichloro-compound (3·2 g.), m.p. 116°, crystallised as yellow needles from the cooled extract. Degutis and Bieksa,[6] who used thionyl chloride in this reaction, give m.p. 112—113°.



NN-*Bis*-(2-*chloroethyl*)-m-*phenylenediamine*.— Tin(II) chloride (70 g.) was added to a stirred solution of *NN*-bis-(2-chloroethyl)-*m*-nitroaniline (20 g.) in conc. hydrochloric acid (40 c.c.) at 0°. After 1 hr., the buff precipitate was collected, washed with conc. hydrochloric acid, then dissolved in ice–water (100 c.c.) and cautiously made slightly alkaline with N-sodium hydroxide at 0°. Extraction with ether then furnished the amine (12·0 g.), m.p. 60° (lit.,[6] 59—60°).

p-*Cyclohexylphenyl Chloroformate*.—A solution of *p*-cyclohexylphenol (5·8 g.) in 2N-sodium hydroxide (20 c.c.) was slowly added to a stirred saturated solution of carbonyl chloride in toluene (40 c.c.) at 0°. The toluene layer was then separated, dried, and evaporated to an oil which partly solidified on storage at 0°. The solid, freed from the oil by filtration, gave needles of *bis*-p-*cyclohexylphenyl carbonate* (1·2 g.), m.p. 80—81° [from petroleum (b.p. 60—80°)], $\nu_{max.}$ 1775 and 1895 cm.$^{-1}$ (Found: C, 79·7; H, 8·3. $C_{25}H_{30}O_3$ requires C, 80·0; H, 8·0%).

The oily filtrate was the crude chloroformate, $\nu_{max.}$ 1770 cm.$^{-1}$, with very weak absorption at 1895 cm.$^{-1}$ (carbonate impurity). It was characterised by reaction with aniline in ether, which gave p-*cyclohexylphenyl* N-*phenylcarbamate* as needles [from petroleum (b.p. 100—120°)], m.p. 142—143°, $\nu_{max.}$ 1745 and 3460 cm.$^{-1}$ (Found: C, 77·4; H, 7·3; N, 4·6. $C_{19}H_{21}NO_2$ requires C, 77·25; H, 7·2; N, 4·7%).

m-*Methoxycarbonylphenyl Chloroformate*.—A solution of methyl *m*-hydroxybenzoate (3·8 g.) in quinoline (3·3 g.) was added dropwise to a stirred saturated solution of carbonyl chloride in benzene (30 c.c.) at 0°. The mixture was stirred overnight, then freed from excess of carbonyl chloride by aeration, washed with 2N-hydrochloric acid, dried, and concentrated below 30° under reduced pressure to an oil (3·9 g.). This crude chloroformate, $\nu_{max.}$ (film) 1712 and 1770 cm.$^{-1}$, was characterised by reaction with aniline in benzene to give m-*methoxycarbonylphenyl* N-*phenylcarbamate*, m.p. 113—115° [from benzene–petroleum (b.p. 40—60°)], $\nu_{max.}$ 1720, 1750, and 3450 cm.$^{-1}$ (Found: C, 66·6; H, 4·8; N, 5·2. $C_{15}H_{13}NO_4$ requires C, 66·4; H, 4·8; N, 5·2%).

o-*Benzyloxycarbonylphenyl Chloroformate*.—Prepared from benzyl salicylate (5·7 g.) in quinoline (3·3 g.), by the method just described, the crude chloroformate (6·0 g.) showed $\nu_{max.}$ (film) 1705 and 1775 cm.$^{-1}$ and reacted with aniline to give o-*benzyloxycarbonylphenyl* N-*phenylcarbamate* as chunky crystals [from petroleum (b.p. 100—120°)], m.p. 88—91°, $\nu_{max.}$ 1710, 1750, and 3430 cm.$^{-1}$ (Found: C, 72·6; H, 5·0; N, 3·9. $C_{21}H_{17}NO_4$ requires C, 72·6; H, 4·9; N, 4·0%).

Urethanes from NN-*Bis*(2-*chloroethyl*)-p-*phenylenediamine*.—(i) *General method*. Phenyl chloroformate[13] (1·6 g.) was added to a stirred mixture of *NN*-bis-(2-chloroethyl)-*p*-phenylenediamine hydrochloride[14] (2·7 g.), pyridine (1·6 g.), and benzene (50 c.c.) at 0°. After 1 hr., the mixture was washed with 2N-hydrochloric acid, then with aqueous sodium hydrogen carbonate and with water, dried, and concentrated under reduced pressure to give a solid. Recrystallisation from benzene afforded phenyl *N*-*p*-(bis-2-chloroethylamino)phenylcarbamate (2·4 g.) as needles, m.p. 124—125°, identical with the compound prepared[2] by a different route.

(ii) *p*-Cyclohexylphenyl chloroformate (0·6 g.) and the amine hydrochloride (0·7 g.) under similar conditions gave *p-cyclohexylphenyl* N-p-(bis-2-*chloroethylamino*)*phenylcarbamate*, which gave needles, m.p.124—125° [from petroleum (b.p. 100—120°)], $\nu_{max.}$ 1740 and 3450 cm.$^{-1}$ (Found: C, 64·1; H, 6·8; Cl, 16·1; N, 6·1. $C_{23}H_{28}Cl_2N_2O_2$ requires C, 63·5; H, 6·5; Cl, 16·3; N, 6·4%).

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(iii) *p*-Methoxycarbonylphenyl chloroformate [4a] ($\nu_{max.}$ 1720 and 1785 cm.$^{-1}$) (0·8 g.) and the amine hydrochloride (1·0 g.) similarly gave p-*methoxycarbonylphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (IV) (1·5 g.), m.p. 143—145° (from benzene), $\nu_{max.}$ 1710, 1745, and 3420 cm.$^{-1}$, (Found: C, 55·3; H, 4·7; N, 6·8. $C_{19}H_{20}Cl_2N_2O_4$ requires C, 55·5; H, 4·9; N, 6·8%).

When a solution of this methyl ester (1·2 g.) in acetic acid (7·5 c.c.) and concentrated hydrochloric acid (7·5 c.c.) was boiled under reflux for 35 min. and then cooled and diluted with ice–water (100 c.c.), a solid was precipitated which gave p-*carboxyphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (V) (1·0 g.), m.p. 178—180° [from ethyl acetate–petroleum (b.p. 40—60°)], $\lambda_{max.}$ (Nujol) 1680, 1720, and 3340 cm.$^{-1}$ (Found: C, 54·6; H, 4·4; Cl, 17·75. $C_{18}H_{18}Cl_2N_2O_4$ requires C, 54·3; H, 4·6; Cl, 17·8%).

(iv) *m*-Methoxycarbonylphenyl chloroformate (2·1 g.) and the amine hydrochloride (2·7 g.) gave m-*methoxycarbonylphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (IX) (2·9 g.), m.p. 137—138° (from benzene), $\nu_{max.}$ 1720, 1740, and 3420 cm.$^{-1}$ (Found: C, 55·45; H, 4·8; N, 6·7%).

Hydrolysis of this methyl ester (0·9 g.), as described for the *p*-isomer, gave m-*carboxyphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (X) (0·7 g.), m.p. 160—162° (from benzene), $\nu_{max.}$ 1710, 1740, and 3430 cm.$^{-1}$ (Found: C, 54·4; H, 4·5; Cl, 17·8; N, 7·1. $C_{18}H_{18}Cl_2N_2O_4$ requires C, 54·3; H, 4·6; Cl, 17·8; N, 7·05%).

(v) *o*-Methoxycarbonylphenyl chloroformate [4b] ($\nu_{max.}$ 1720 and 1780 cm.$^{-1}$) (1·3 g.) and the amine hydrochloride (1·35 g.), but with the pyridine replaced by triethylamine (1·0 g.), gave o-*methoxycarbonylphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (VI) (1·8 g.), m.p. 107—108° (from benzene), $\nu_{max.}$ 1720, 1740, and 3440 cm.$^{-1}$ (Found: C, 55·5; H, 4·6; Cl, 17·1; N, 7·0. $C_{19}H_{20}Cl_2N_2O_4$ requires C, 55·5; H, 4·9; Cl, 17·2; N, 6·8%).

When this methyl ester was boiled with acetic–hydrochloric acid, as already described, even after 2 hr. it was recovered (40%); none of the corresponding acid could be isolated.

(vi) *o*-Benzyloxycarbonylphenyl chloroformate (2·1 g.) and the amine hydrochloride (2·0 g.) gave an oil from which, by chromatography on silica, with chloroform–petroleum (b.p. 60—80°) (7 : 3) as eluant, a solid was obtained. Recrystallisation from benzene–petroleum (b.p. 40—60°) gave o-*benzyloxycarbonylphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (VII) (2·0 g.), m.p. 78—80°, $\nu_{max.}$ 1705, 1715, and 3450 cm.$^{-1}$ (Found: C, 61·7; H, 4·9; Cl, 14·8; N, 5·7. $C_{25}H_{24}Cl_2N_2O_4$ requires C, 61·6; H, 5·0; Cl, 14·5; N, 5·75%).

This benzyl ester (1·0 g.) in methanol (40 c.c.), containing one drop of concentrated hydrochloric acid, was shaken in hydrogen with 10% palladium–charcoal (50 mg.). After 6 hr., when absorption had ceased, the solution was filtered and evaporated to a viscous oil, which was dissolved in benzene, washed, and recovered; it then crystallised. Recrystallisation from benzene gave o-*carboxyphenyl* N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (VIII) (0·3 g.), m.p. 73—74°, $\nu_{max.}$ 1700, 1730, and 3450 cm.$^{-1}$ (Found: C, 59·7; H, 5·1; Cl, 15·6; N, 5·7. $C_{18}H_{18}Cl_2N_2O_4,C_6H_6$ requires C, 60·6; H, 5·1; Cl, 14·9; N, 5·9%).

(vii) Crude *N*-benzyloxycarbonyl-*O*-chloroformyl-DL-serine methyl ester [5a] [$\nu_{max.}$ (film) 1735 and 1765 cm.$^{-1}$], was characterised by reaction with aniline; the N-*benzyloxycarbonyl*-O-(N-*phenylcarbamoyl*)-DL-*serine methyl ester* had m.p. 74—75° [from benzene–petroleum (b.p. 40—60°)] (Found: C, 60·9; H, 5·4; N, 7·3. $C_{19}H_{20}N_2O_6$ requires C, 61·3; H, 5·4; N, 7·5%).

Reaction of the crude chloroformate (3·0 g.) with the amine hydrochloride (2·6 g.) under the standard conditions gave N-*benzyloxycarbonyl*-O-[N-p-(*bis*-2-*chloroethylamino*)-*phenylcarbamoyl*]-DL-*serine methyl ester* (XI) (2·3 g.), m.p. 100—102° [from benzene–petroleum (b.p. 40—60°)], $\nu_{max.}$ 1718, 1735, and 3410 cm.$^{-1}$ (Found: C, 54·1; H, 5·2; Cl, 13·9; N, 7·9. $C_{23}H_{27}Cl_2N_3O_6$ requires C, 53·9; H, 5·3; Cl, 13·8; N, 8·2%).

This carbamate (2·5 g.) in methanol (75 c.c.) and concentrated hydrochloric acid (0·7 c.c.) was hydrogenolysed over 5% palladium–charcoal (0·1 g.). After 12 hr., absorption had ceased, and the filtered solution was evaporated. The residue, taken up in methanol and precipitated by ether, afforded O-[N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamoyl*]-DL-*serine methyl ester* (XII) (1·6 g.) as a dihydrochloride dihydrate, $\nu_{max.}$ 1680sh, 1735, and 3400—3600 cm.$^{-1}$, which had no sharp m.p. (Found: C, 37·4; H, 5·7; Cl, 29·3; N, 8·6. $C_{15}H_{21}Cl_2N_3O_4,2HCl,2H_2O$ requires C, 37·0; H, 5·6; Cl, 29·1; N, 8·6%).

(viii) Crude *N*-benzyloxycarbonyl-*O*-chloroformyl-DL-serine benzyl ester [5a] ($\nu_{max.}$ 1720 and 1770 cm.$^{-1}$) (4·8 g.) and the amine hydrochloride (3·9 g.) gave N-*benzyloxycarbonyl*-O-[N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamoyl*]-DL-*serine benzyl ester* (XIII) (5·2 g.), which after recrystallisation from benzene and then from carbon tetrachloride had m.p. 129°, $\nu_{max.}$ 1720 and 3410 cm.$^{-1}$ (Found: C, 59·05; H, 5·3; Cl, 12·5; N, 6·7. $C_{29}H_{31}Cl_2N_3O_6$ requires C, 59·2; H, 5·3; Cl, 12·1; N, 7·1%).

Hydrogenolysis of this benzyl ester (1·5 g.) in methanol (25 c.c.) and ethyl acetate (25 c.c.) over 5% palladium–charcoal (30 mg.) gave N-*benzyloxycarbonyl*-O-[N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamoyl*]-DL-*serine* (XIV) (0·8 g.), m.p. 133—135° (from ethyl acetate), $\nu_{max.}$ 1715, 3400, and 3670 cm.$^{-1}$ (Found: C, 53·1; H, 5·0; N, 7·9. $C_{22}H_{25}Cl_2N_3O_6$ requires C, 53·0; H, 5·0; N, 8·4%).

Hydrogenolysis of the same benzyl ester (1·0 g.) in methanol (50 c.c.) and concentrated hydrochloric acid (0·2 c.c.) over 10% palladium–charcoal (20 mg.) gave O-[N-p-*bis*-2-*chloroethylamino*)*phenylcarbamoyl*]-DL-*serine* (XV), which crystallised from methanol–ether as the hydrochloride hydrate, m.p. 123—126°, $\nu_{max.}$ 1720, 1740, and 3400—3600 cm.$^{-1}$ (Found: C, 40·6; H, 5·2; Cl, 25·2; N, 10·0. $C_{14}H_{19}Cl_2N_2O_3,HCl,H_2O$ requires C, 40·2; H, 5·3; Cl, 25·4; N, 10·0%).

(ix) Crude *N*-benzyloxycarbonyl-*O*-chloroformyl-DL-threonine benzyl ester,[5a] ($\nu_{max.}$ 1720 and 1765 cm.$^{-1}$) was characterised by reaction with aniline to give N-*benzyloxycarbonyl*-O-(N-*phenylcarbamoyl*)-DL-*threonine benzyl ester*, m.p. 107—108° [from benzene–petroleum (b.p. 40—60°)], $\nu_{max.}$ 1730 and 3410 cm.$^{-1}$ (Found: C, 67·75; H, 5·55; N, 5·9. $C_{26}H_{26}N_2O_6$ requires C, 67·5; H, 5·7; N, 6·1%).

The crude chloroformate (4·6 g.) and the amine hydrochloride (4·1 g.) under the standard conditions gave N-*benzyloxycarbonyl*-O-[N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamoyl*-DL-*threonine benzyl ester* (XVI) (5·9 g.), m.p. 91° (from benzene), $\nu_{max.}$ 1715, 1735, and 3410 cm.$^{-1}$ (Found: C, 59·7; H, 5·5; Cl, 12·0; N, 6·65. $C_{30}H_{33}Cl_2N_3O_6$ requires C, 59·8; H, 5·5; Cl, 11·8; N, 7·0%).

Hydrogenolysis of this benzyl ester (3·0 g.) in methanol (150 c.c.) and concentrated hydrochloric acid (0·5 c.c.), over 10% palladium–charcoal (50 mg.) gave a solid (1·2 g.) on evaporation of the filtered solution. Recrystallisation from methanol-ether gave O-(N-p-(*bis*-2-*chloroethylamino*)-

phenylcarbamoyl-DL-*threonine* (XVII) as a dihydrochloride dihydrate, $\nu_{max.}$ (Nujol) 1720, 1740, and 3400—3600 cm.$^{-1}$, which had no sharp m.p. (Found: C, 37·8; H, 5·5; N, 8·6. $C_{15}H_{21}Cl_2N_3O_4$,HCl,H_2O requires C, 37·0; H, 5·6; N, 8·6%).

(x) Crude *N*-benzyloxycarbonyl-*O*-chloroformyl-L-tyrosine benzyl ester [5b] was characterised by reaction with aniline. After crystallisation from benzene–petroleum (b.p. 40—60°) the N-*benzyloxycarbonyl*-O-(N-*phenylcarbamoyl*)-L-*tyrosine benzyl ester* had m.p. 135—136° (Found: C, 71·0; H, 5·3; N, 5·3. $C_{31}H_{28}N_2O_6$ requires C, 71·0; H, 5·4; N, 5·3%).

Reaction of the crude chloroformate (3·0 g.) with the amine hydrochloride (2·1 g.) gave an oil from which, by chromatography on silica, with chloroform–petroleum (b.p. 60—80°) (7 : 3) as eluant, two solids were obtained. One was *NN'*-bis-*p*-(bis-2-chloroethylamino)phenylurea [2] (0·8 g.), m.p. and mixed m.p. 207°; the other was N-*benzyloxycarbonyl*-O-[N-p-(*bis*-2-*chloroethylamino*)*phenylcarbamoyl*]-L-*tyrosine benzyl ester* (XVIII) (0·75 g.), m.p. 38—42° [from petroleum (b.p. 40—60°)], $\nu_{max.}$ 1720, 1740, and 3450 cm.$^{-1}$ (Found: C, 63·3; H, 5·3; Cl, 10·6; N, 6·2. $C_{35}H_{35}Cl_2N_3O_6$ requires C, 63·2; H, 5·3; Cl, 10·7; N, 6·3%).

Urethanes from NN-*Bis*-(2-*chloroethyl*)-m-*phenylenediamine*.—Except that the free amine, not the hydrochloride, was used, the procedures were the same as described for the *p*-amino-compound.

(i) Ethyl chloroformate (0·27 g.) and the amine (0·5 g.) gave *ethyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (XIX; Y = Et) (0·2 g.), m.p. 86—87° [from benzene–petroleum (b.p. 40—60°)], $\nu_{max.}$ 1720 and 3450 cm.$^{-1}$ (Found: C, 51·4; H, 5·7; Cl, 23·25; N, 9·2. $C_{13}H_{18}Cl_2N_2O_2$ requires C, 51·1; H, 5·9; Cl, 23·25; N, 9·2%).

(ii) Isopropyl chloroformate (0·12 g.) and the amine (0·25 g.) gave *isopropyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (XIX; Y = Pr^i) (0·2 g.), m.p. 104—105° [from petroleum (b.p. 100—120°)], $\nu_{max.}$ 1720 and 3440 cm.$^{-1}$ (Found: C, 52·5; H, 6·4; Cl, 22·2; N, 8·7. $C_{14}H_{20}Cl_2N_2O_2$ requires C, 52·7; H, 6·3; Cl, 22·2; N, 8·8%).

(iii) Phenyl chloroformate (0·8 g.) and the amine (1·15 g.) gave *phenyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (XIX; Y = Ph) (1·1 g.), m.p. 107—108° (from benzene), $\nu_{max.}$ 1745 and 3450 cm.$^{-1}$ (Found: C, 58·1; H, 5·2; Cl, 19·9; N, 7·8. $C_{17}H_{18}Cl_2N_2O_2$ requires C, 57·8; H, 5·1; Cl, 20·1; N, 7·9%).

(iv) *p*-Cyclohexylphenyl chloroformate (0·6 g.) and the amine (0·6 g.) gave p-*cyclohexylphenyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (XIX; Y = *p*-cyclohexylphenyl) (0·6 g.), m.p. 138—139° [from benzene–petroleum (b.p. 60—80°)], $\nu_{max.}$ 1750 and 3440 cm.$^{-1}$ (Found: C, 63·0; H, 6·4; Cl, 16·3; N, 6·5. $C_{23}H_{28}Cl_2N_2O_2$ requires C, 63·4; H, 6·5; Cl, 16·3; N, 6·4%).

(v) *m*-Methoxycarbonylphenyl chloroformate (2·1 g.) and the amine (2·3 g.) gave m-*methoxycarbonylphenyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (2·2 g.), m.p. 118° (from benzene) (Found: C, 58·2; H, 4·9; Cl, 15·8; N, 6·0. $C_{19}H_{20}Cl_2N_2O_4$,0·5C_6H_6 requires C, 58·7; H, 5·15; Cl, 15·75; N, 6·2%). Recrystallisation from petroleum (b.p. 100—120°) gave the solvent-free compound, m.p. 114°, $\nu_{max.}$ 1720, 1750, and 3450 cm.$^{-1}$ (Found: C, 55·8; H, 4·8; Cl, 17·0; N, 6·7. $C_{19}H_{20}Cl_2N_2O_4$ requires C, 55·5; H, 4·9; Cl, 17·2; N, 6·8%).

Hydrolysis of this methyl ester, as already described for similar compounds, gave m-*carboxyphenyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate*, m.p. 128—131° [from ethyl acetate–petroleum (b.p. 40—60°)], $\nu_{max.}$ (Nujol) 1680, 1720, and 3400 cm.$^{-1}$ (Found: Cl, 18·0. $C_{18}H_{18}Cl_2N_2O_4$ requires Cl, 17·8%).

(vi) *o*-Benzyloxycarbonylphenyl chloroformate (2·0 g.) and the amine (1·8 g.) gave o-*benzyloxycarbonylphenyl* N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamate* (2·1 g.), m.p. 99° (from benzene), $\nu_{max.}$ 1720, 1750, and 3440 cm.$^{-1}$ (Found: C, 61·9; H, 4·9; Cl, 14·4; N, 5·9. $C_{25}H_{24}Cl_2N_2O_4$ requires C, 61·6; H, 5·0; Cl, 14·5; N, 5·8%).

(vii) *N*-Benzyloxycarbonyl-*O*-chloroformyl-DL-serine benzyl ester (0·6 g.) and the amine (0·5 g.) gave an oil, from which a solid (0·4 g.) was obtained by chromatography on alumina with chloroform–petroleum (b.p. 60—80°) (7 : 3) as eluant. Recrystallisation from benzene–petroleum (b.p. 40—60°) gave N-*benzyloxycarbonyl*-O-[N-m-(*bis*-2-*chloroethylamino*)*phenylcarbamoyl*]-DL-*serine benzyl ester*, m.p. 95—96°, $\nu_{max.}$ 1705—1745 and 3430 cm.$^{-1}$ (Found: C, 59·2; H, 5·3; Cl, 12·0; N, 7·05. $C_{29}H_{31}Cl_2N_3O_6$ requires C, 59·2; H, 5·3; Cl, 12·05; N, 7·1%).

Bis-[p-(*bis*-2-*chloroethylamino*)*anilide*] *of Terephthalic Acid* (XXI).—A solution of terephthaloyl chloride (1·0 g.) in benzene (10 c.c.) was added to a stirred solution of *NN*-bis-(2-chloroethyl)-*p*-phenylenediamine hydrochloride (2·7 g.) and pyridine (1·6 g.) in benzene (30 c.c.) at 0°. The product was isolated as described for the reaction of phenyl chloroformate with the same amine hydrochloride, and gave the *derivative* as plates, m.p. 187—190° (from acetone), $\nu_{max.}$ (Nujol) 1640 and 3300 cm.$^{-1}$ (Found: C, 56·3; H, 5·0; Cl, 23·05; N, 9·3. $C_{28}H_{30}Cl_4N_4O_2$ requires C, 56·4; H, 5·1; Cl, 23·8; N, 9·4%).

p-*Methoxycarbonylbenzoyl Chloride*.—Dry methanol (0·8 c.c.) was slowly added to a solution of terephthaloyl chloride (4·1 g.) in benzene (50 c.c.) at 0°. The mixture was stored at 0° overnight and then distilled to give a fraction (2·7 g.), b.p. 130° (bath)/0·8 mm., which solidified, m.p. 38° (lit.,[8-10] 38—40°, 130° (*sic*), and 54—55° respectively), $\nu_{max.}$ 1725 and 1770 cm.$^{-1}$.

N-p-(NN-*bis*-2-*chloroethylamino*)*phenyl*-p-*methoxycarbonylbenzamide* (XX).—Reaction of the foregoing acid chloride (2·0 g.) with *NN*-bis-(2-chloroethyl)-*p*-phenylenediamine hydrochloride (2·7 g.) under the usual conditions gave, on chromatography (alumina–chloroform) the diamide (XXI) (2·1 g.) already described above, m.p. 188—190°; and small prisms of the substituted *benzamide* (0·5 g.), m.p. 158—159° (from chloroform), $\nu_{max.}$ 1670, 1715, and 3410 cm.$^{-1}$ (Found: C, 57·25; H, 5·1; N, 6·9. $C_{19}H_{20}Cl_2N_2O_3$ requires C, 57·7; H, 5·1; N, 7·1%).

N-p-(NN-*Bis*-2-*chloroethylamino*)*phenylphthalimide* (XXII).—Reaction of *o*-methoxycarbonylbenzoyl chloride [11] [from methyl hydrogen phthalate (1·8 g.)] with *NN*-bis-(2-chloroethyl)-*p*-phenylenediamine hydrochloride (2·7 g.), in the same way, gave the *imide* (2·9 g.), needles (from chloroform), m.p. 169—170°, $\nu_{max.}$ 1705, 1730sh, 1750, and 1775 cm.$^{-1}$ (Found: C, 59·3; H, 4·3; Cl, 19·3; N, 7·9. $C_{18}H_{16}Cl_2N_2O_2$ requires C, 59·5; H, 4·4; Cl, 19·5; N, 7·7%).

N-m-(NN-*Bis*-2-*chloroethylamino*)*phenylphthalimide* (XXIII).—In a similar fashion, the same acid chloride [from methyl hydrogen phthalate (0·9 g.)] condensed with *NN*-bis(2-chloroethyl)-*m*-phenylenediamine (1·1 g.) to give the *imide* (1·4 g.), plates (from chloroform), m.p. 138—139°, $\nu_{max.}$ 1705sh, 1720, 1760, and 1780 cm.$^{-1}$ (Found: C, 59·5; H, 4·4; Cl, 19·75; N, 7·3%).

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